Asymmetric Allylic Alkylation of Acyclic Allylic Ethers with Organolithium Reagents

Perez, Manuel; Fananas-Mastral, Martin; Hornillos, Valentin; Rudolph, Alena; Bos, Pieter H.; Harutyunyan, Syuzanna R.; Feringa, Ben L.

Published in:
Chemistry : a European Journal

DOI:
10.1002/chem.201202251

Publication date:
2012

CHEMISTRY
A EUROPEAN JOURNAL

Supporting Information

Asymmetric Allylic Alkylation of Acyclic Allylic Ethers with Organolithium Reagents

Manuel Pérez, Martín Fañanás-Mastral, Valentín Hornillos, Alena Rudolph, Pieter H. Bos, Syuzanna R. Harutyunyan,* and Ben L. Feringa*[a]

chem_201202251_sm_miscellaneous_information.pdf

Table of Contents **S2**

General Procedures:

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reactions were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Carbon assignments are based on APT ^{13}C-NMR experiments. Optical rotations were measured on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantiomeric excesses were determined by HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector or by capillary GC analysis (HP 6890, CP-Chiralsil-Dex-CB column (25 m x 0.25 mm) or Chiraldex G-TA (30 m x 0.25 mm x 0.25 μm) using flame ionization detector.

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. Dichloromethane was dried and distilled over calcium hydride; toluene, THF and *n*-hexane were dried and distilled over sodium. All copper-salts ($CuBr{\bullet}SMe_2$, CuTC, CuI, CuCN, $Cu(OTf)_2$ and $Cu(OTf){\bullet}C_6H_6$) were purchased from Aldrich, and used without further purification. Allyl esters **S1**,**S2** and ethers **S3-S7, 1a, 2a, 1c, 2c, 2f** and **2g** were prepared following literature procedures (**S1**,[1] **S2**,[2] **S3**,[3] S**4**,[4] S5,[5] S**6**,[6] S**7**,[7] **1a,**[8] **2a,**[9] **1c,**[2] **2c,**[10] **2f**[11] and **2g**[12])**.**

---

[1] Correia, R., De Shong, P., *J. Org. Chem.* **2001,** *66,* 7159-7165.

[2] Fujita, M., Wakita, M., Sugimura, T., *Chem. Commun.*, **2011**, *47*, 3983-3985.

[3] Quach, T.D., Batey, R.A., *Org. Lett.,* **2003**, *5*, 1381-1384.

[4] Fujioaka, H., Kubo, O., Okamoto, K., Senami, K., Okitsu, T., Ohnaka, T., Sawama, Y., Kita, Y., *Heterocycles*, **2009**, *77*, 1089-1110.

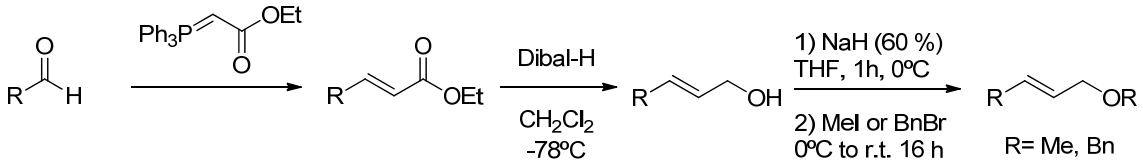
[5] Goff, D.A., Harris, R.E., Bottaro, J.C., Bedford, C., *J. Org. Chem.*, **1986**, *51(24)*, 4711-4714.

Organolithium reagents were purchased from Aldrich (MeLi 1.6 M in Et_2O), (*n*-HexLi (2.3 M in *n*-hexane), (PhLi 1.8 M in dibutyl ether), or from Acros (*n*-BuLi 1.6 M in *n*-hexane). (*R*,*R*)-TaniaPhos (**L4**) was purchased from Aldrich. Phosphoramidite ligands **L1**,[13] (**L2**, **L6-8**),[14] **L3**[15] and **L5**[16] were prepared as reported in the literature.

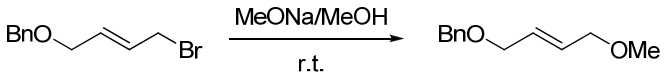
Racemic products were synthesized by reaction of the allyl ethers **1/2** and the corresponding organolithium reagent at -78°C in CH_2Cl_2 in the presence of $CuBr{\bullet}SMe_2$ (5.5 mol%) and a racemic mixture of **L1** (11 mol%).

<u>Preparation of allylic ethers 1b, 2b, 1d, 1e, 1g and 2d</u>:

Allyl ethers **1b, 2b, 1d, 1e** and **2d** were synthesized from the corresponding aldehydes by a three-step procedure; involving a classic Wittig olefination/Dibal-H reduction/etherification sequence.



The allylic ether **1g** was synthesized from the corresponding allylic bromide[17] by treatment with a 25 % solution of MeONa in MeOH.



---

[6] Barbero, M., Cadamuro, S., Dughera, S., Venturello, P., *Synthesis*, **2008**, 1379-1388; Salehi, P., Lranpoor, N., Kargar, F., *Tetrahedron,* **1998**, *54*, 943-948.

[7] Kurita, T., Aoki, F., Mizumoto, T., Maejima, T., Esaki, H., Maegawa, T., Monguchi, Y., Sajiki, H. *Chem.–Eur. J.* **2008**, *14*, 3371–3379.

[8] Matsubara, R., Jamison, T.F., *J. Am. Chem. Soc.*, **2010**, *132*, 6880–6881.

[9] Chakraborti A.K., Chankeshwara, S.V., *J. Org. Chem.*, **2009**, *74*, 1367-1370.

[10] Maki, B.E., Chan, A., Scheidt, K.A., *Synthesis*, **2008**, *8*, 1306-1315.

[11] Kim, J.D., Lee, M.H., Han, G., Park, H., Zee, O.P., Jung, Y.H. *Tetrahedron,* **2001**, *57*, 8257-8266.

[12] Hachiya, I., Matsumoto, T., Inagaki, T., Takahashi, A., Shimizu, M. *Heterocycles*, **2010**, *82*, 449-460.

[13] Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623.

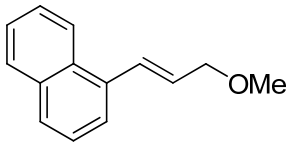
[14] Tissot-Croset, K.; Polet, D.; Gille, S.; Hawner, C.; Alexakis, A. *Synthesis* **2004**, 2586–2590.

[15] Choi, Y. H.; Choi, J. Y.; Yang, H. Y.; Kim, Y. H. *Tetrahedron: Asymmetry* **2002**, *13*, 801-804.

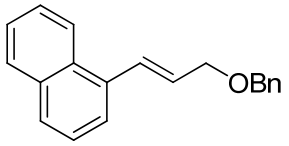
[16] Shintani, R.; Park, S.; Duan, W.-L.; Hayashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5901-5903.

[17] Kottirsch,G., Koch,G., Feifel,R., Neumann, U., *J. Med. Chem.*, **2002**, *45*, 2289–2293.

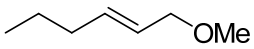
Spectroscopic data of allyl ethers **1**/**2** that have not been previously reported are presented below.



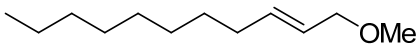
(*E*)-1-(3-methoxyprop-1-enyl)naphthalene (1b): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.13 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.51 – 7.34 (m, 3H), 6.33 (t, *J* = 5.8 Hz, 1H), 6.29 (t, *J* = 5.8 Hz, 1H), 4.18 (d, *J* = 5.8 Hz, 2H), 3.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 134.5, 133.6, 131.2, 129.4, 129.2, 128.5, 128.0, 126.0, 125.7, 125.6, 123.9, 123.8, 73.2, 58.0.



(*E*)-1-(3-(benzyloxy)prop-1-enyl)naphthalene (2b): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.24 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.3 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.68 – 7.38 (m, 8H), 6.50 (t, *J* = 5.9 Hz, 1H), 6.46 (t, *J* = 5.9 Hz, 1H), 4.76 (s, *J* = 13.6 Hz, 2H), 4.41 (dd, *J* = 5.9, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 138.4, 134.6, 133.7, 131.2, 129.6, 129.4, 128.6, 128.5 (2C), 128.1, 127.9 (2C), 127.8, 126.1, 125.8, 125.7, 124.0, 123.9, 72.3, 71.0.

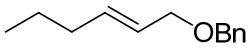


(E)-1-methoxyhex-2-ene (1d): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.69 (dt, *J* = 14.4, 6.6 Hz, 1H), 5.54 (dt, *J* = 14.0, 6.2 Hz, 1H), 3.86 (d, *J* = 6.2 Hz, 2H), 3.31 (s, 3H), 2.02 (q, *J* = 6.9 Hz, 2H), 1.45 – 1.36 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 135.0, 125.9, 73.4, 57.5, 34.3, 22.6, 14.0.

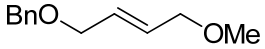


(*E*)-1-methoxyundec-2-ene (1e): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.68 (dt, *J* = 14.1, 6.6 Hz, 1H), 5.52 (dt, *J* = 15.3, 6.2 Hz, 1H), 3.84 (d, *J* = 6.2 Hz, 2H), 3.29 (s, 3H), 2.02 (q, *J*

= 6.9 Hz, 2H), 1.46 – 1.20 (m, 12H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 134.9, 126.0, 73.3, 57.5, 32.3, 31.8, 29.4, 29.2, 29.2, 29.1, 22.6, 14.0.



(*E*)-((hex-2-enyloxy)methyl)benzene (2d): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.58-7.27 (m, 5H), 5.83 (dt, *J* = 14.4, 6.0 Hz, 1H), 5.72 (dt, *J* = 15.4, 6.1 Hz, 1H), 4.61 (s, 2H), 4.09 (d, *J* = 6.0 Hz, 2H), 2.16 (dd, *J* = 13.7, 6.7 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 138.4, 134.5, 128.2 (2C), 127.6 (2C), 127.3, 126.3, 71.8, 70.8, 34.3, 22.1, 13.6.



(*E*)-((4-methoxybut-2-enyloxy)methyl)benzene (1g): ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.43-7.28 (m, 5H), 5.87 – 5.80 (m, 2H), 4.52 (s, 2H), 4.05 (d, *J* = 4.1 Hz, 2H), 3.94 (d, *J* = 4.0 Hz, 2H), 3.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 135.6, 127.0, 126.7, 125.8 (2C), 125.2 (2C), 125.0, 69.8, 69.5, 67.4, 55.3.

General procedure for the copper-catalyzed allylic alkylation of allyl ethers 1-2 with organolithium reagents.

A Schlenk tube equipped with septum and stirring bar was charged with CuTC (0.01 mmol, 1.90 mg, 5 mol%) and the appropriate ligand (0.022 mmol, 11 mol%). Dry dichloromethane (0.5 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. In another Schlenk tube BF_3•OEt_2 (0.4 mmol, 50 μL, 2.0 eq) was added to a solution of TMSOTf (1.2 mmol, 215 μL, 6.0 eq) in dichloromethane (0.5 mL) at -80 ºC, and the resulting "BF_2OTf"[18] solution was stirred for 15 min. Then, the corresponding allyl ether **1-2** (0.2 mmol) in CH_2Cl_2 (1 mL) was added at -80 °C to the copper/ligand solution prepared earlier and subsequently a solution of "BF_2OTf" in dichloromethane (0.4 mmol, 600 μL, 2.0 eq) was added. In a separate Schlenk tube, the corresponding organolithium reagent (0.30 mmol, 1.5 eq) was diluted with hexane (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture

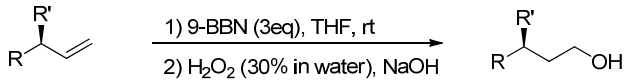
[18] Myers,E.D., Butts, C.P., Aggarwal, V.K. *Chem. Commun.* **2006**, 4434.

over 2 h using a syringe pump. The reaction was quenched with a saturated aqueous NH_4Cl solution (2 mL) and the mixture was warmed up to room temperature, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using different mixtures of *n*-pentane:Et_2O as the eluent.

Note: Gas chromatography analysis was carried out to determine the branched:linear (b:l) ratio on a sample obtained after aqueous extraction with dichloromethane, which has been passed through a short plug of silica gel to remove transition metal residues.

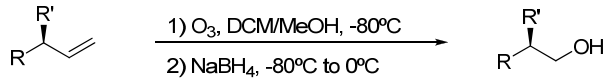
Note 2: In some cases it was necessary to carry out a hydroboration/oxidation or an ozonolysis/reduction protocol to determine the enantiomeric ratios of the products (*vide infra*).

General protocol for the hydroboration and oxidation of alkenes 3



To a suspension of the alkene (1 mmol) in dry THF (3 mL), 9-BBN in THF (0.5 M, 3 mmol, 3 eq) was added and the mixture was stirred at room temperature for 2 h. Then, ethanol (4.5 mL), an aqueous solution of NaOH (6.0 M, 1.2 mL) and H_2O_2 (30 % in water, 7 mL) were added at 0 ºC and the reaction mixture was stirred for 1 h. The reaction was quenched with brine and the mixture extracted with ethyl acetate (3 x 10 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using different mixtures of *n*-pentane:Et_2O as the eluent.

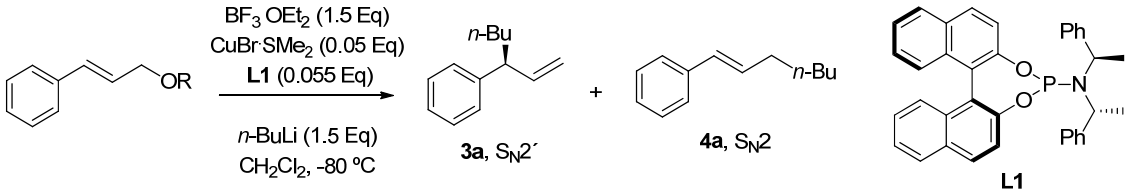
General protocol for the reductive ozonolysis of alkenes 3



Ozone was bubbled for 30 min through a solution of the alkene (0.081 mmol) in a mixture of DCM (2 mL) and MeOH (2 mL) at -78 °C. After stirring for 15 min (solution stays blue) the reaction mixture was purged with nitrogen. Sodium borohydride (7.68 mg, 0.203 mmol, 2.5 eq) was added and the mixture was warmed to room temperature and stirred for 2h. The reaction was quenched by addition of a 1M aqueous HCl solution. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were dried with sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using different mixtures of *n*-pentane:Et_2O as the eluent.

Screening results:

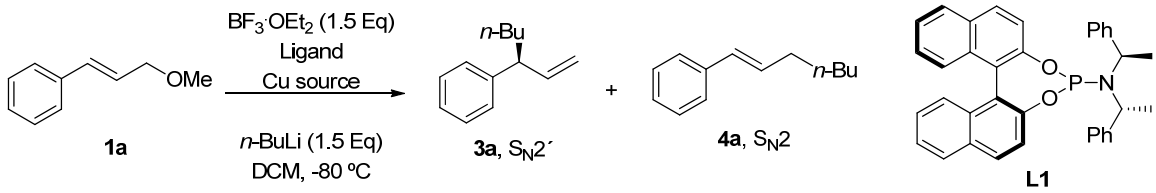
Table S1. Screening of allylic leaving groups.



Entry[a]	OR	Ligand	Lewis Acid	3a:4a	3a, e.r.	Conv.
1	**S1**, -OBz	**L1**	$BF_3{\cdot}OEt_2$	-	-	50%[b]
2	**S2**, -OAc	**L1**	$BF_3{\cdot}OEt_2$	100:0	-	45%[c]
3	**S3**, -OPh	**L1**	$BF_3{\cdot}OEt_2$	-	-	0%
4	**S4**, -OTHP	**L1**	$BF_3{\cdot}OEt_2$	-	-	0%
5	**S5**, -OMOM	**L1**	$BF_3{\cdot}OEt_2$	0:100	-	40%
6	**S6**, -O*i*-Pr	**L1**	$BF_3{\cdot}OEt_2$	12:88	-	55%
7	**S7**, -OTBS	**L1**	$BF_3{\cdot}OEt_2$	8:92	70:30	60%
8	**1a**, -OMe	**L1**	$BF_3{\cdot}OEt_2$	55:45	84:16	100%
9	**2a**, -OBn	**L1**	$BF_3{\cdot}OEt_2$	37:63	91:9	100%

[a]Conditions: 0.2 mmol of allylic ether, 1.5 eq of *n*-BuLi diluted in hexane, 0.1 M in CH_2Cl_2, 2 h addition time, 1.5 eq of $BF_3{\cdot}OEt_2$. [b]Recovered the corresponding allylic alcohol. [c]Recovered 40% of allylic alcohol and 5% of **10a**.

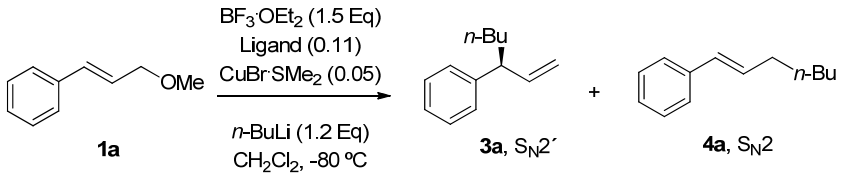
Table S2. Copper and Lewis acid effect



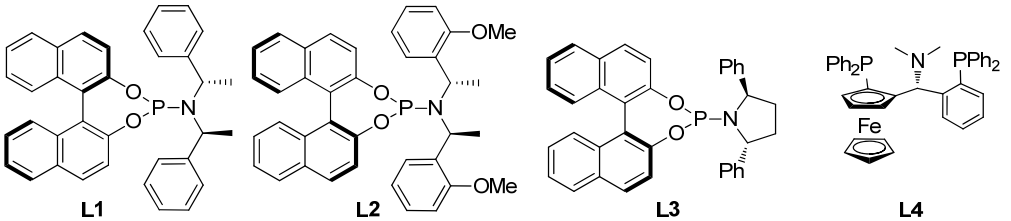
Entry[a]	$CuBr{\cdot}SMe_2$ (Eq)	$BF_3{\cdot}OEt_2$	Ligand	Conv.
1	-	1,5 Eq	-	0%
2	-	-	-	0%
3	0.05 Eq	-	**L1**	0%
4	0.05 Eq	1,5 Eq	**L1**	100%

[a] Conditions: 1.5 eq of *n*-BuLi diluted in hexane, 0.1 M in CH_2Cl_2, 2 h addition time and 1.5 eq of $BF_3{\cdot}OEt_2$

Table S3. Ligand screening.



1a **3a**, S_N2' + **4a**, S_N2

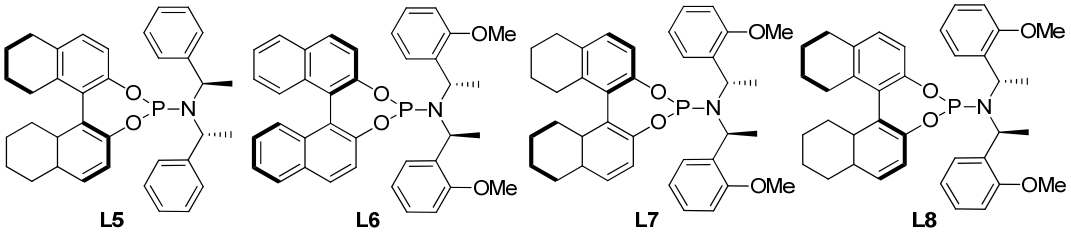


L1 63/37 (S_N2'/S_N2) e.r.: 90:10

L2 80/20 (S_N2'/S_N2) e.r.: 3:97

L3 70/30 (S_N2'/S_N2) e.r.: 77:23

L4 0/100 (S_N2'/S_N2) (15% of conversion) e.r.: -



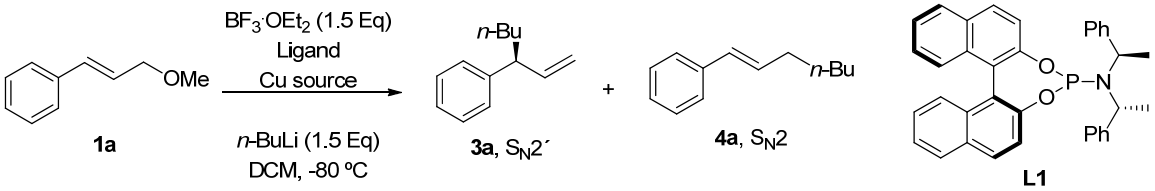
L5 75/25 (S_N2'/S_N2) e.r.: 8:92

L6 48/52 (S_N2'/S_N2) e.r.: 81:19

L7 50/50 (S_N2'/S_N2) e.r.: 65:35

L8 50/50 (S_N2'/S_N2) e.r.: 9:91

Table S4. Copper salts screening.

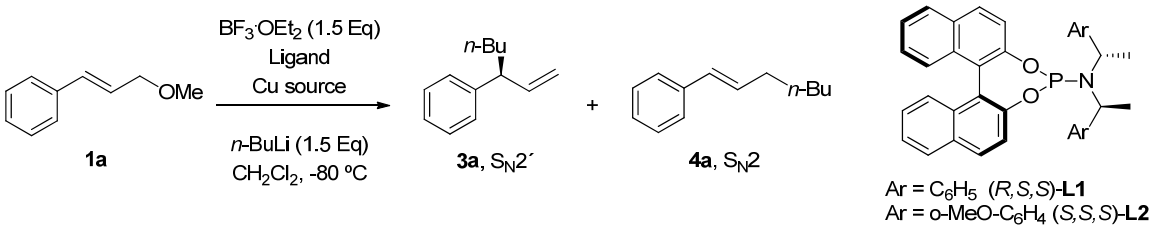


1a **3a**, S_N2' + **4a**, S_N2 **L1**

Entry	Lig./Cu	Cu Salt	Lig.	S_N2':S_N2	e.r.	Conv.
1	2/1	$CuBr{\cdot}SMe_2$	**L1**	63%:37%	90:10	100%
2	2/1	CuTC	**L1**	67%:33%	91:9	70%
3	2/1	CuI	**L1**	-:-	-	0%
4	2/1	CuCN	**L1**	-:-	-	0%
5	2/1	$Cu(OTf)_2$	**L1**	52%:48%	89:11	100%
6	2/1	$Cu(OTf)\ C_6H_6$	**L1**	55%:45%	93:7	100%

[a] Conditions: 1.5 eq of *n*-BuLi diluted in hexane, 0.1 M in CH_2Cl_2, 2 h addition time and 1.5 eq of $BF_3{\cdot}OEt_2$

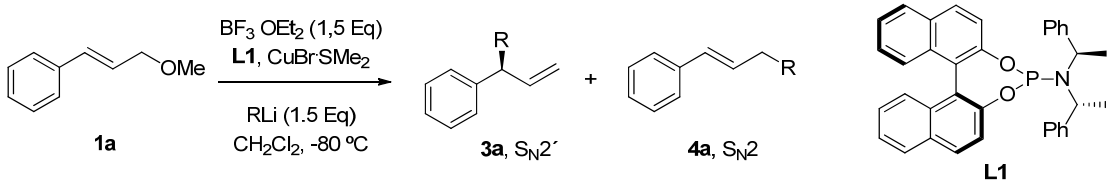
Table S5. Cu/Ligand ratio.



Entry	Lig/Cu	Cu Salt	Ligand	S_N2':S_N2	e.r.	Conv.
1	1/1	CuBr·SMe_2	**L1**	55%:45%	84:16	100%
2	2/1	CuBr·SMe_2	**L1**	63%:37%	90:10	100%
3	1/1	CuBr·SMe_2	**L2**	73%:27%	97:3	100%
4	2/1	CuBr·SMe_2	**L2**	80%:20%	97:3	100%

[a] Conditions: 1.5 eq of *n*-BuLi diluted in hexane, 0.1 M in CH_2Cl_2, 2 h addition time and 1.5 eq of BF_3·OEt_2.

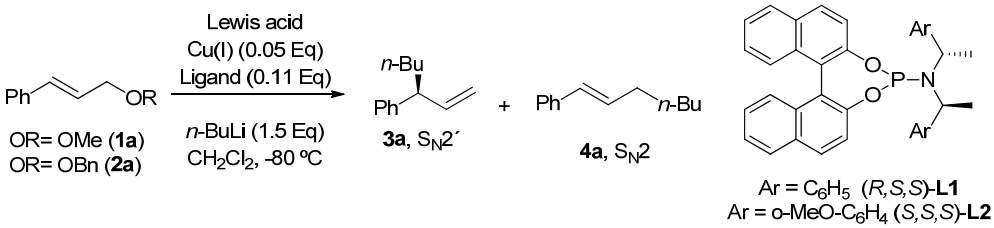
Table S6. Organolithium dilution (co-solvent) studies.



Entry	RLi	Co-solvent	S_N2':S_N2	e.r.	Conv.
1	*n*-BuLi (1.6 M in Hexanes)	0,25 M in Hexane/Et_2O	50%:50%	-	5%
2	*n*-BuLi (1.6 M in Hexanes)	1,6 M in Hexane	33%:66%	78:26	100%
3	*n*-BuLi (1.6 M in Hexanes)	0,25 M in Hexane	63%:37%	90:10	100%
4	*n*-BuLi (1.6 M in Hexanes)	0,10 M in Hexane	48%:52%	85:15	100%
5	MeLi (1,6 M in Et_2O)	0,25 M in Hexane/Et_2O	-:-	-	0%
6	PhLi (1,8 M in Bu_2O)	0,25 M in Hexane/Et_2O	-:-	-	0%

[a] Conditions: 1.5 eq of RLi diluted, 0.1 M in CH_2Cl_2, 2 h addition time, 1.5 eq of BF_3·OEt_2 and **L1**/CuBr·SMe_2 ratio was 2/1.

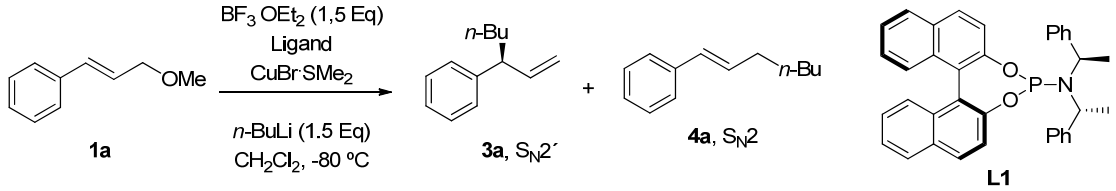
Table S7. Lewis acid screening.



Entry[a]	Lewis acid[b]	OR	Cu salts	Lig	3a: 4a	3a, e.r.	Conv.
1	$BF_3{\cdot}OEt_2$	OMe	$CuBrSMe_2$	**L1**	63:37	90:10	100%
2	BBr_3	OMe	$CuBrSMe_2$	**L1**	-	-	100%[c]
3	BCl_3	OMe	$CuBrSMe_2$	**L1**	-	-	100%[c]
4	$B(OEt)_3$	OMe	$CuBrSMe_2$	**L1**	-	-	0%
5	$B(Et)_3$	OMe	$CuBrSMe_2$	**L1**	-	-	0%
6	$BF_3{\cdot}$ *t*-BuOMe	OMe	$CuBrSMe_2$	**L1**	-	-	0%
7	TMSCl	OMe	$CuBrSMe_2$	**L1**	-	-	0%
8	TMSOTf	OMe	$CuBrSMe_2$	**L1**	-	-	0%
9	$BF_3{\cdot}OEt_2$(2.0 eq) / TMSCl (4.0 eq)	OMe	$CuBrSMe_2$	**L1**	50:50	89:11	90%
10	$BF_3{\cdot}OEt_2$(1.5 eq) / TMSOTf (3.0 eq)	OMe	$CuBrSMe_2$	**L1**	75:25	93:7	100%
11	$BF_3{\cdot}OEt_2$(1.5 eq) / TMSOTf (3.0 eq)	OMe	$CuBrSMe_2$	**L2**	87:13	97:3	72%[d]
12	$BF_3{\cdot}OEt_2$(2.0 eq) / TMSOTf (4.0 eq)	OMe	CuTC	**L2**	91:9	98:2	80%[d]
13	$BF_3{\cdot}OEt_2$(2.0 eq) / TMSOTf (6.0 eq)	OMe	CuTC	**L2**	91:9	99:1	80%[d]
14	$BF_3{\cdot}OEt_2$(2.0 eq) / TMSOTf (6.0 eq)	OBn	CuTC	**L2**	95:5	99:1	86%[d]

[a]Conditions: 0.2 mmol of allylic ether, 1.5 eq of *n*-BuLi diluted in hexane, 0.1 M in CH_2Cl_2, 2 h addition time. [b]1.5 eq of Lewis acid. The mixtures of Lewis acids were used in 0.5 mL of CH_2Cl_2 at -80 ºC. [c]Complete conversion was obtained, but the products were the corresponding allylic bromide and chloride, respectively. [d]100% conversion, isolated yield in parenthesis.

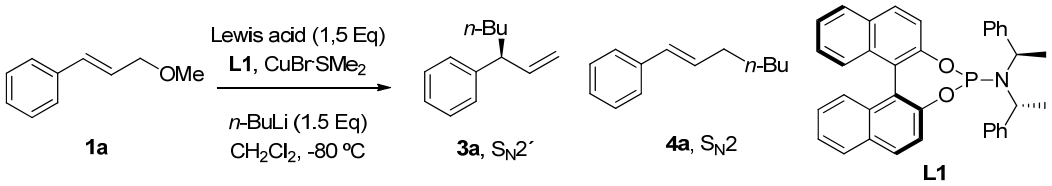
Table S8. Addition procedure.



Entry	*n*-BuLi	Lig/Cu	S_N2':S_N2	e.r.	Addition procedure	Conv.
1	0,25 M in Hexane/CH_2Cl_2	1/1	25%:75%	94:6	Slow addition of $BF_3{\cdot}OEt_2$ in CH_2Cl_2	65%
2	0,25 M Hexane	2/1	50%:50%	85:15	Double addition: a) $BF_3{\cdot}OEt_2$ in CH_2Cl_2 b) *n*-BuLi in hexanes (different syringes)	100%

[a] Conditions: 1.5 eq of *n*-BuLi diluted , 0.1 M in CH_2Cl_2, 2 h addition time, 1.5 eq of $BF_3{\cdot}OEt_2$ and $CuBr{\cdot}SMe_2$.

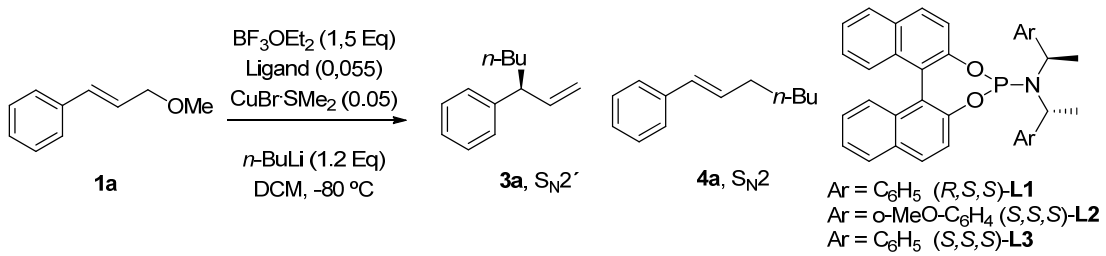
Table S9. Number of equivalents of Lewis acid.



Entry	Eq of BF_3OEt_2	Lig./Cu	S_N2'/S_N2	e.e.	Conv.
1	**0.95**	1/1	50%/50%	68%	85%
2	**1,5**	1/1	55%/45%	68%	100%
3	**2,0**	1/1	55%/45%	71%	100%

[a] Conditions: 1.5 eq of *n*-BuLi diluted in hexane, 0.1 M in CH_2Cl_2, 2 h addition time, $BF_3{\cdot}OEt_2$ and $CuBr{\cdot}SMe_2$.

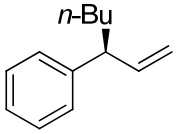
Table S10. Addition time.



Entry	Addition time	Ligand	S_N2'/S_N2	e.e.	Conv.
1	1h	**L1**	45%/55%	68%	100%
2	2h	**L1**	55%/45%	68%	100%
3	5h	**L1**	50%/50%	79%	100%
4	2h	**L2**	73%/27%	94%	100%
5	5h	**L2**	70%/30%	93%	100%
6	1h	**L3**	55%/45%	0 %	100%
7	2h	**L3**	50%/55%	0 %	100%

[a] Conditions: 1.5 eq of *n*-BuLi diluted in hexane, 0.1 M in CH_2Cl_2, 1.5 eq of Lewis acid and $CuBr{\cdot}SMe_2$

Compound characterization

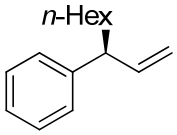


(+)-(*S*)-hept-1-en-3-ylbenzene (3a): Colorless oil obtained from **2a** after 2 h addition of *n*-BuLi as a 95:5 mixture of **3a** and **4a** after column chromatography (SiO_2, *n*-pentane), [86% yield, 99:1 e.r.].

The physical data were identical in all respects to those previously reported.[19]

$[\alpha]_D^{20}$ = +49.0 (*c* = 1.0, $CHCl_3$), [lit.[19] (97:3 e.r.): $[\alpha]_D^{20}$ = +47 (*c* = 0.5, $CHCl_3$)].

Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 80°C for 80 min, then 1°C/min to 140°C (hold for 5 min), then 10°C/min to 180°C (final temp), retention times (min.): 82.6 (minor) and 83.6 (major).



(+)-(*S*)-non-1-en-3-ylbenzene (3b): Colorless oil obtained from **2a** as a 96:4 mixture of **3b** and **4b** after column chromatography (SiO_2, *n*-pentane), [92% yield, > 99:1 e.r.].

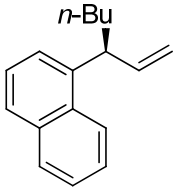
The physical data were identical in all respects to those previously reported.[19,20]

$[\alpha]_D^{20}$ = +28.0 (*c* = 1.0, $CHCl_3$), [lit.[19] (> 99:1 e.r.): $[\alpha]_D^{20}$ = +29.2 (*c* = 1.0, $CHCl_3$)].

The enantiomeric ratio was determined for the primary alcohol obtained following the hydroboration and oxidation protocol of the terminal double bond (*vide supra*). Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, *n*-heptane/*i*-PrOH 99:1, 40 °C, 210 nm, retention times (min.): 18.7 (major) and 21.0 (minor).

[19] a) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409–411. b) Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Nature Chem.* **2011**, *3*, 377.

[20] Arai, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489–5493.

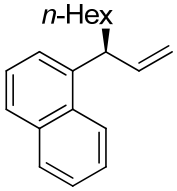


(-)-(*S*)-1-(hept-1-en-3-yl)naphthalene (3c): Colorless oil obtained from **2b** after column chromatography (SiO_2, *n*-pentane), [84% yield, 99:1 e.r.].

The physical data were identical in all respects to those previously reported.[19]

$[\alpha]_D^{20}$ = -8.0 (*c* = 1.0, $CHCl_3$), [lit.[19] (98:2 e.r.): $[\alpha]_D^{20}$ = -7.6 (*c* = 0.9, $CHCl_3$)].

Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane/*i*-PrOH 99.75:0.25, 40 °C, 240 nm, retention times (min.): 17.2 (major) and 20.2 (minor).



(-)-1-(non-1-en-3-yl)naphthalene (3d): Colorless oil obtained from **2b** as a 98:2 mixture of **3d** and **4d** after column chromatography (SiO_2, *n*-pentane), [80% yield, 98:2 e.r.].

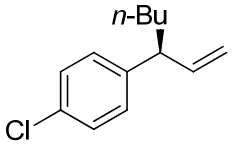
^{1}H NMR (400 MHz, $CDCl_3$): 8.14 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.32 (m, 4H), 6.16 – 6.01 (m, 1H), 5.16 – 5.03 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 1H), 1.96 –1.77 (m, 2H), 1.47– 1.17 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 142.1, 140.7, 134.0, 131.7, 128.9, 126.6, 125.7, 125.5, 125.3, 123.9, 123.4, 114.4, 44.3, 35.3, 31.8, 29.4, 27.7, 22.6, 14.1.

$[\alpha]_D^{20}$ = -2.0 (*c* = 1.0, $CHCl_3$).

Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane/*i*-PrOH 99.75:0.25, 40 °C, 240 nm, retention times (min.): 16.7 (major) and 22.7 (minor). HRMS (ESI+, *m/z*): calcd for $C_{19}H_{24}$ $[M+H]^+$: 253.19508; found: 253.19712.

In accordance with the results obtained in the related allylic alkylations, the absolute configuration of this compound is assumed to be (*S*), analogous to the related products.

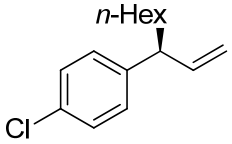


(+)-(*S*)-1-chloro-4-(hept-1-en-3-yl)benzene (3e): Colorless oil obtained from **2c** as a 97:3 mixture of **3e** and **4e** after column chromatography (SiO_2, *n*-pentane), [81% yield, 99:1 e.r.].

The physical data were identical in all respects to those previously reported.[19]

$[\alpha]_D^{20}$ = +35.0 (*c* = 1.0, $CHCl_3$), [lit.[19] (99:1 e.r.): $[\alpha]_D^{20}$ = +36.6 (*c* = 1.0, $CHCl_3$)].

Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 130°C for 60 min, then 10°C/min to 175°C (hold for 5 min, final temp), retention times (min.): 18.8 (minor) and 19.1 (major).

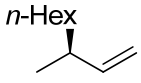


(+)-(*S*)-1-chloro-4-(non-1-en-3-yl)benzene (3f): Colorless oil obtained from **2c** as a 90:10 mixture of **3f** and **4f** after column chromatography (SiO_2, *n*-pentane), [79% yield, >99:1 e.r.].

The physical data were identical in all respects to those previously reported.[19,21]

$[\alpha]_D^{20}$ = +22.8 (*c* = 1.0, $CHCl_3$), [lit.[19] (> 99:1 e.r.): $[\alpha]_D^{20}$ = +18.0 (*c* = 1.0, $CHCl_3$)].

Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 100:0, 40 °C, 215 nm, retention times (min): 7.9 (major) and 9.6 (minor).

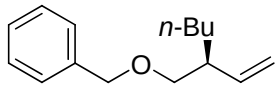


(*S*)-3-methylnon-1-ene (3i): Colorless solution in CH_2Cl_2 was obtained from **2f** as a 97:3 mixture of **3i** and **4i** [conversion of 100%, 95:5 e.r.].

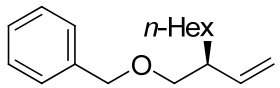
The high volatility of the products **3i** and **4i** did not allow removing all the solvents after worked up, impeding the determination of an accurate isolated yield.

[21] Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.* **2008**, *73*, 1983–1986.

Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25m x 0.25mm) initial temp. 55ºC for 30 min (final temp), retention times (min.): 25.3 (major) and 27.3 (minor). In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (*S*), analogous to the related products.

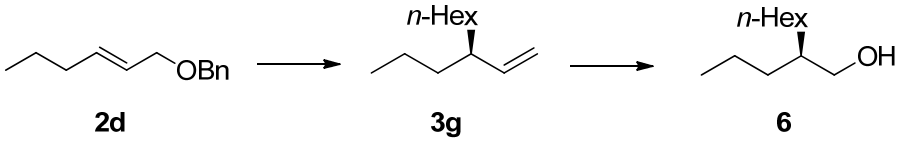


(+)-(*S*)-(((2-vinylhexyl)oxy)methyl)benzene (3j): Colorless oil obtained from **1g** after column chromatography (SiO_2, *n*-pentane), [51% yield, conversion of 60%, 93:7 e.r.]. The physical data were identical in all respects to those previously reported.[19] $[\alpha]_D^{20}$ = +10.0 (*c* = 1.0, $CHCl_3$), [lit.[19] (97:3 e.r.): $[\alpha]_D^{20}$ = +18.5 (*c* = 2.2, $CHCl_3$)]. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 100:0, 40 °C, retention times (min): 11.4 (minor) and 13.0 (major).



(+)-(*S*)-(((2-vinyloctyl)oxy)methyl)benzene (3k): Colorless oil obtained from **2g** after column chromatography (SiO_2, *n*-pentane), [45% yield, conversion of 55%, 98:2 e.r.]. The physical data were identical in all respects to those previously reported.[19b] $[\alpha]_D^{20}$ = +12.0 (*c* = 1.0, $CHCl_3$), [lit.[19b] (93:7 e.r.): $[\alpha]_D^{20}$ = +8.2 (*c* = 1.0, $CHCl_3$)]. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 100:0, 40 °C, retention times (min): 11.4 (minor) and 13.1 (major).

Synthesis of (*S*)-Arundic acid:



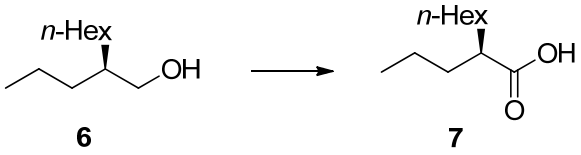
(-)-(S)-2-propyloctan-1-ol (6): *n*-Hexyllithium was added to **2d** following the general procedure for the copper-catalyzed allylic alkylation of allyl ethers (see p.S6). A 95:5 mixture of **3g** and **4g** [conversion of 100%, >99:1 e.r.] was obtained.

The high volatility of the products **3g** and **4g** did not allow to completely remove the solvents after work up, impeding the determination of an accurate isolated yield.

The mixture of **3g** and **4g** in CH_2Cl_2 (10 mL) as obtained directly from the work up of the allylic alkylation, was diluted with MeOH (5 mL) and treated by reductive ozonolysis (*vide supra*). After column chromatography (SiO_2, 10% Et_2O/*n*-pentane) the alcohol **6** was obtained in 72% yield (overall yield for the two steps) and with >99:1 e.r.

The physical data were identical in all respects to those previously reported.[22]

$[\alpha]_D^{20}$ = -3.8 (*c* = 0.75, MeOH), Enantiomeric ratio was determined after preparation of (*S*)-Arundic acid **7** (*vide infra*)**.**



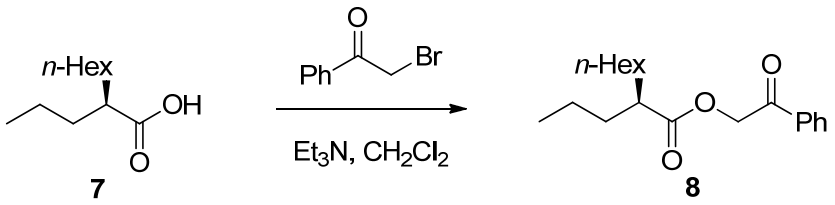
(+)-(*S*)-2-propyloctanoic acid (7): To a solution of alcohol **6** (18 mg; 96 μmol) in a mixture of CH_3CN:H_2O (1:1) (2 mL), were added iodobenzene diacetate (60 mg; 192 μmol) and TEMPO (1.5 mg; 9.6 μmol). The mixture was stirred at room temperature for 10 h. Subsequently the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated by rotatory

[22] Gualandi, A., Emer, E., Guiteras-Capdevila, M., Cozzi, P.G. *Angew. Chem. Int. Ed.* **2011**, *50*, 7842.

evaporation. The obtained residue was purified by column chromatography (SiO_2, 20% Et_2O/*n*-pentane), yielding the desired compound [94% yield, >99:1 e.r.].
The physical data were identical in all respects to those previously reported.[22,23]
$[\alpha]_D^{20}$ = +5.1 (*c* = 1.0, EtOH), [lit.[23] (94:6 er): $[\alpha]_D^{20}$ = +5.5 (c = 0.38, CH_2Cl_2)].
HRMS (ESI+, *m/z*): calcd for $C_{11}H_{23}O_2$ $[M+H]^+$: 187.16926; found: 187.16843.

Determination of the enantiomeric ratio of (*S*)-Arundic acid 7

The enantiomeric ratio was determined by conversion of (*S*)-Arundic acid **7** into the corresponding phenacyl ester **8**.

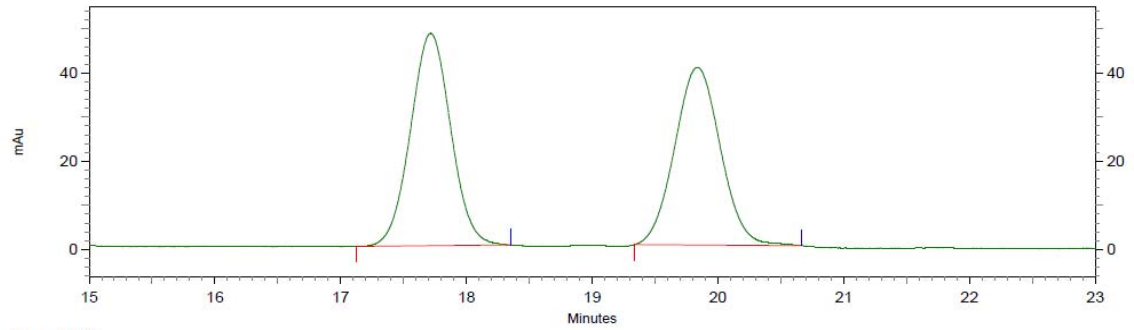


To a solution of (*S*)-Arundic acid **7** (18 mg, 0.097 mmol) in CH_2Cl_2 (2 mL), Et_3N (50 µL, 0.359 mmol) and 2-bromoacetophenone (35 mg, 0.177 mmol) were added and the reaction mixture was stirred at room temperature for 5 h. Then, the solvents were removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, 10% Et_2O/*n*-pentane).
Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, 0.5 mL/min, *n*-heptane/*i*-PrOH 99:1, 40 °C, retention times (min.): 17.7 (major) and 19.8 (minor).

[23] Pelotier, B., Holmes, T., Piva, O. *Tetrahedron: Asymmetry*, **2005**, *16*, 1513.

HPLC traces of 8

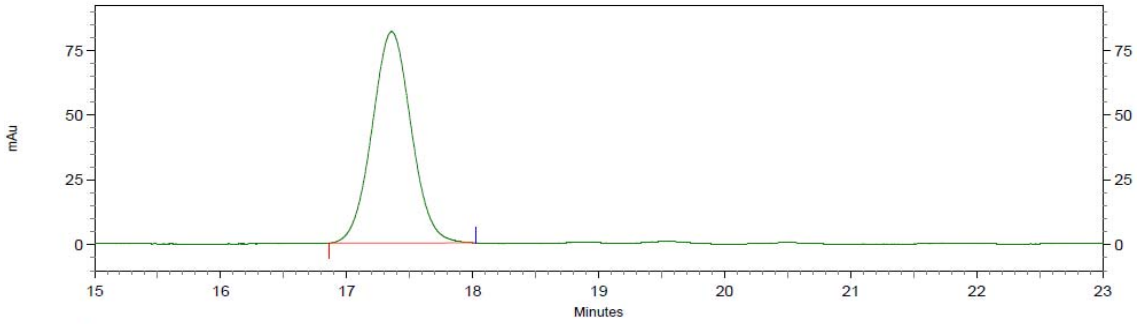
Racemic:



1: 236
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	1	17,716	1076744	51,359
2	2	19,836	1019766	48,641

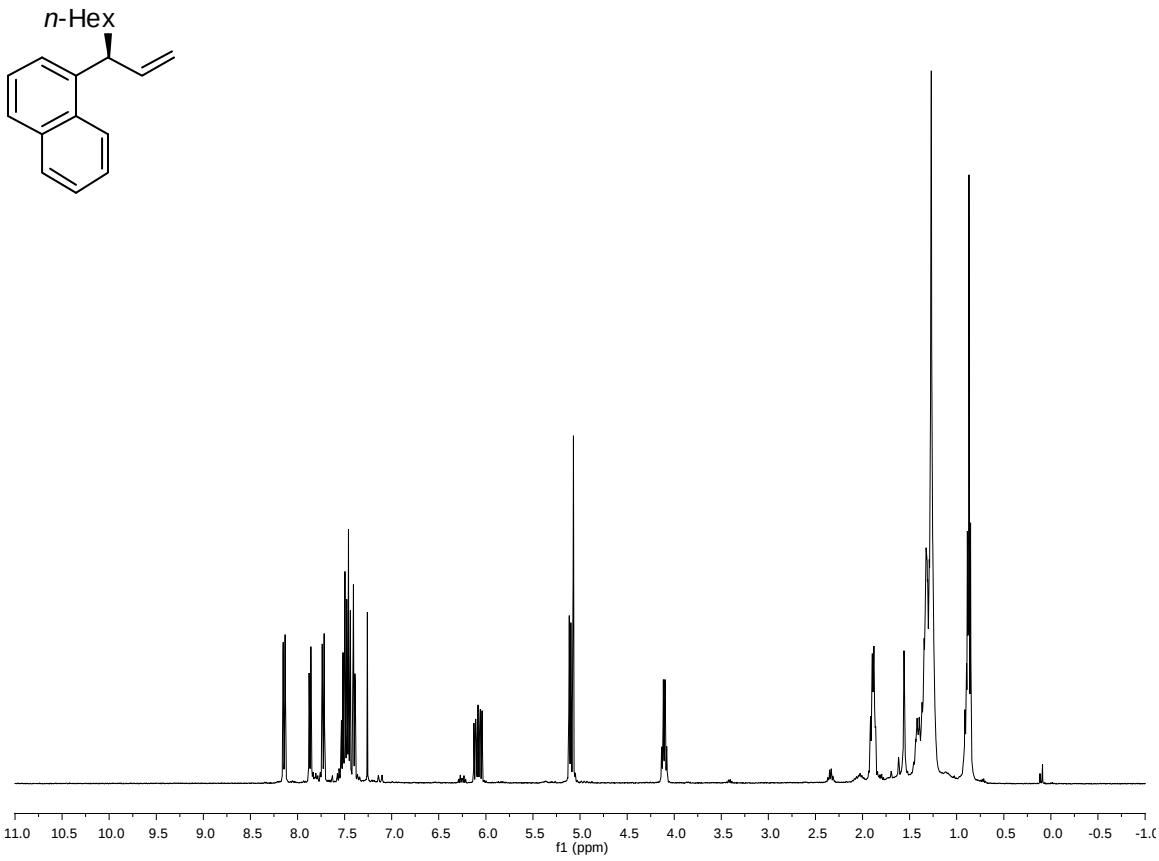
Enantiopure:

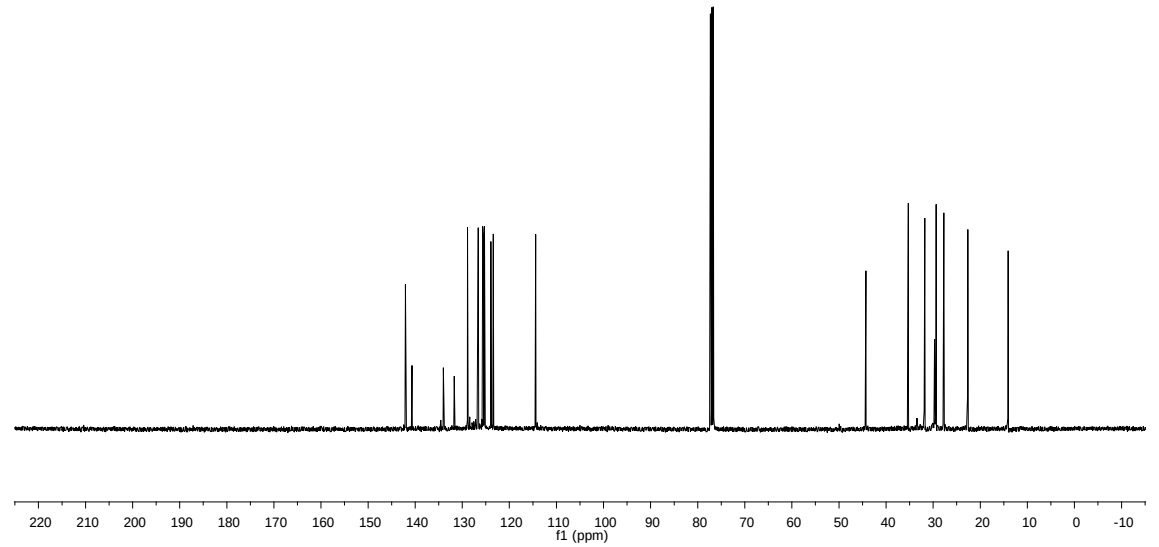


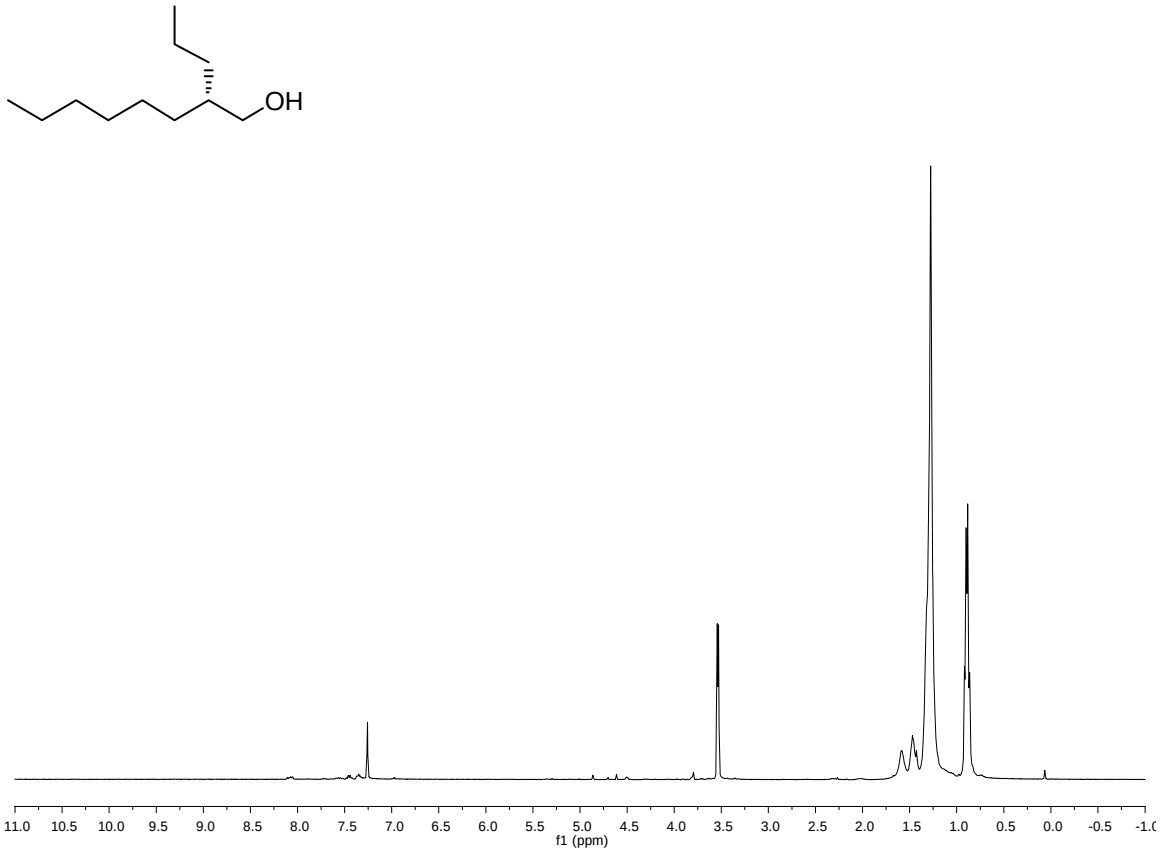
Results

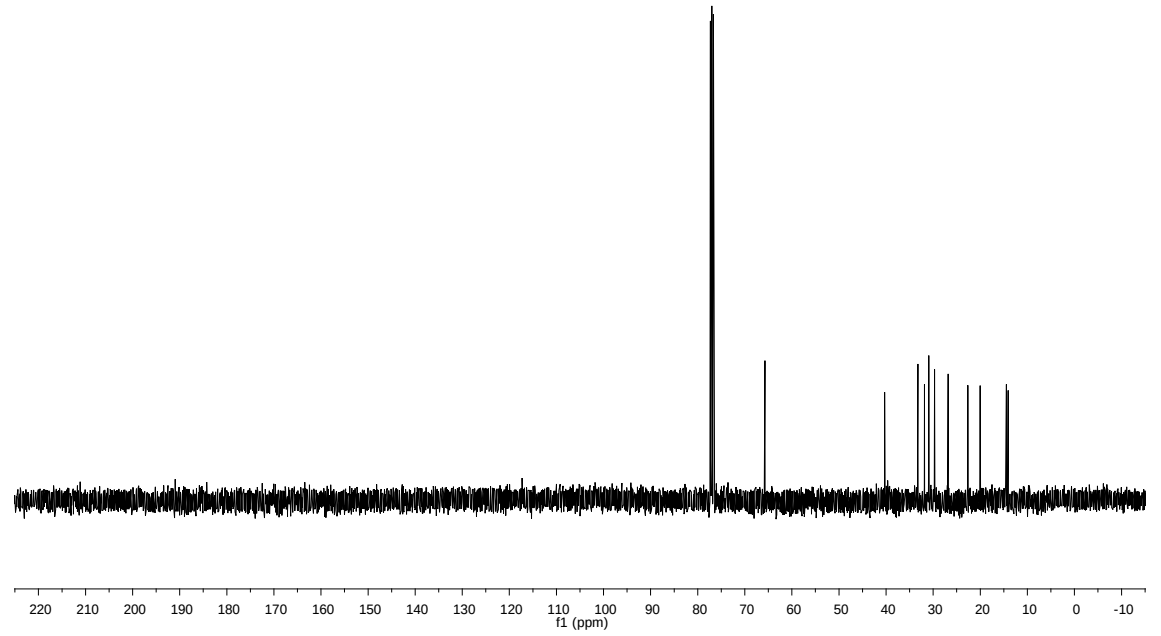
Pk #	Name	Retention Time	Area	Area Percent
1	1	17,356	1764045	100,000

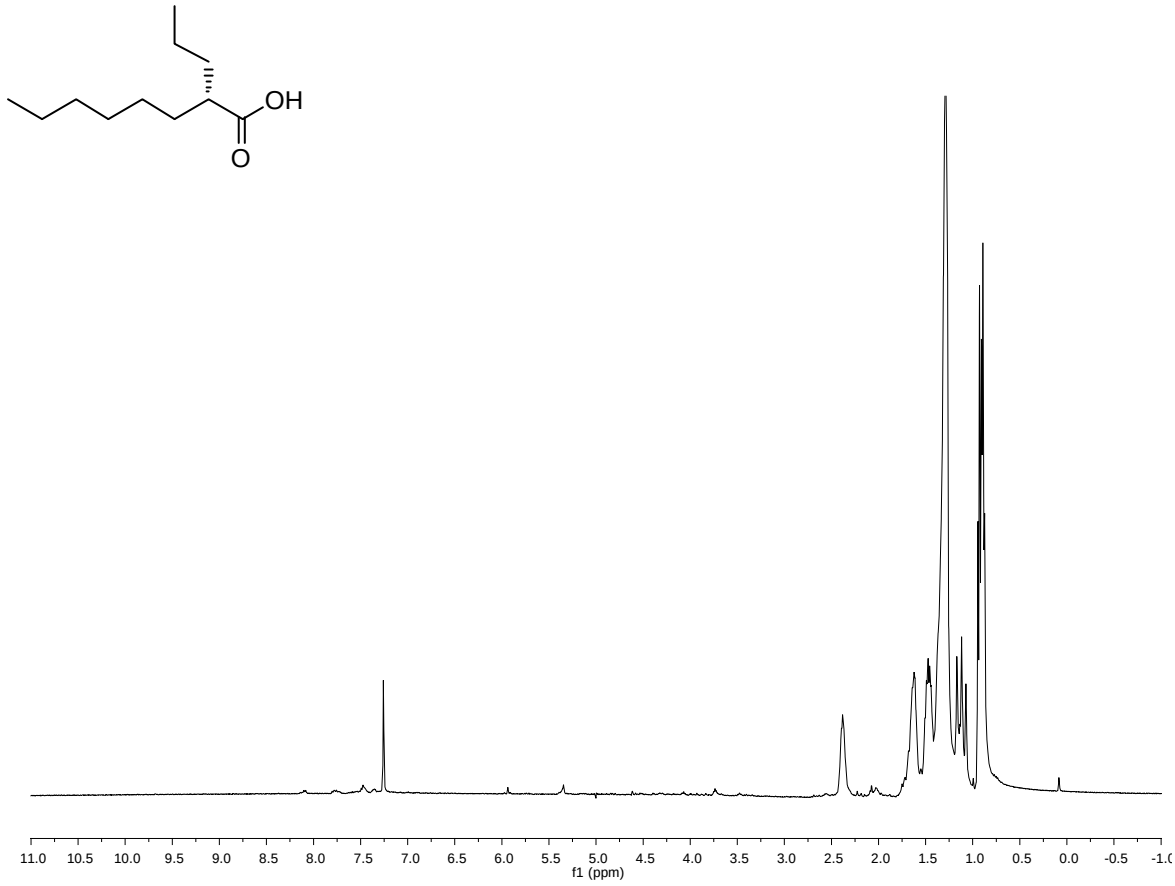
NMR spectra of new compounds and intermediates in the synthesis of (*S*)-Arundic acid

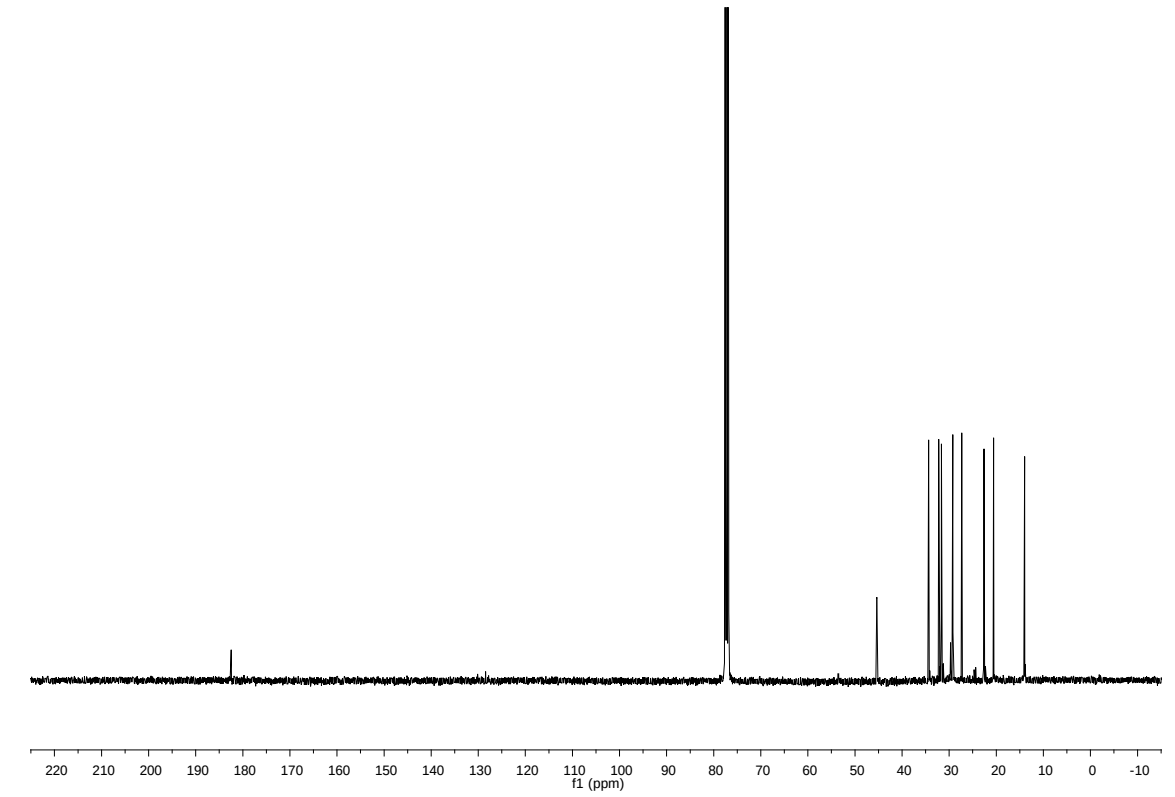

n-Hex
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
O
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)